REMARKS

The Invention

The present invention is directed to methods of treating a neoplasia in a mammal involving administering to the mammal a serum stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion. Administration of the nucleic acid-lipid particle is by injection at a site distal to the neoplasia in the mammal. In some embodiments, a prodrug is also administered to the mammal. In other embodiments, a chemotherapeutic agent is also administered to the mammal.

Status of the Claims

Claims 1-28 are pending. Claims 1-28 stand rejected under 35 U.S.C. §112, first paragraph. This rejection is addressed below.

New claims 35-41 have been added. Support for new claims 36-41 is found throughout the specification and claims as originally filed. Thus, no new matter is added by these amendments.

Applicants request that new claims 36-41 in the present Amendment be entered under 37 C.F.R. § 1.116.

A version of the claims with markings to show changes to the claims are provided in Appendix A. All of the pending claims are provided in Appendix B for the Examiner's convenience.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner maintains the rejection of claims 1-28 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement.

The Examiner alleges that the claims are not enabled for the treatment of any neoplasm comprising the distal administration of any expressible gene fully encapsulated within any lipid-nucleic acid particle. In making this rejection, the Examiner acknowledges that the claims are enabled for treatment effects comprising the administration of the nucleic acid encoding HSV-TK and ganciclovir, which nucleic acid is fully encapsulated in the lipid formulations explicitly disclosed.

The Examiner further alleges that treatment effects are not necessarily provided by a nucleic acid merely because the nucleic acid has not been degraded by nucleases in the serum of an organism. In making this rejection, the Examiner acknowledges that the specification is enabling for the increased stability of fully encapsulated nucleic acids in serum which are present in lipid-nucleic acid particles comprising the formulations 1.1, 1.2, 1.3, 1.4, and 1.5.

As previously explained, a particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without ***undue*** experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. It is important to note that the possibility that some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, MPEP § 2164.01.
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP § 2164.06, citing *In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988).
>
> As MPEP § 2164.02 states, "[a] rigorous or an invariable exact correlation is not required" between a particular model and a specific condition.
>
> As set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments."

Applicants respectfully ***disagree*** with the Examiner's allegation of nonenablement and respectfully submit that the specification provides numerous working examples describing the ***expression*** of nucleic acids in tumor cells after delivery via the lipid-nucleic acid particles used in the methods of the present invention (Examples 8, 9, and

10). The specification also provides numerous working examples of ***actual*** inhibition or prevention of tumor growth after treatment with the lipid-nucleic acid particles of the present invention (Examples 6, 7, 11, 13, 14, and 15). In addition, the specification provides ample guidance for practicing the claimed invention. In particular, the specification provides (1) teachings regarding therapeutic nucleic acids; (2) teachings regarding preparation and properties of lipid-nucleic acid particles; (3) teachings regarding disease indications suitable for treatment using the lipid-nucleic acid particles of the present invention; and (4) teachings regarding administration of lipid-nucleic acid particles (*see, e.g.*, page 10, line 14 to page 14, line 24; page 14, line 25 to page 18, line 31; page 19, line 28, to page 20, line 16; and page 21, lines 20 to page 22, lines 27).

Furthermore, Dr. MacLachlan, in his declaration, explicitly states that, in his scientific opinion as one of skill in the art, the examples in the specification unequivocally demonstrate that (1) nucleic acids encapsulated in the lipid-nucleic acid particles of the invention are ***actually*** expressed in tissues after administration of the particles, and (2) nucleic acids encapsulated in the lipid-nucleic acid particles of the invention ***are*** effective in treating neoplasia (*see,* Declaration ¶7 and ¶8). In particular, Dr. MacLachlan states that administration of the lipid-nucleic acid particles of the present invention reduces tumor size and growth rate and leads to enhanced long term survival. Dr. MacLachlan also affirms that the teachings in the specification provide adequate guidance for one of skill in the art to administer serum stable lipid-nucleic acid particles by injection at a site distal to a neoplasia in a mammal (*see,* Declaration ¶10). Dr. MacLachlan also describes *in vivo* experiments demonstrating that cytokines, tumor suppressor proteins, and cytotoxins are effective in inhibiting tumor growth (*see*, Declaration ¶12). Dr. MacLachlan further describes *in vitro* experiments demonstrating that multiple suicide enzymes are effective in inhibiting tumor cell proliferation (*see*, Declaration ¶12). Finally, Dr. MacLachlan explains that the references cited by the Examiner in the Office Action of April 10, 2001 as allegedly illustrating the state of the art with regard to gene therapy ***support*** the proposition that lipid-nucleic acid particles can effectively be used to deliver therapeutic nucleic acids to neoplasias, *i.e.*, that gene therapy using lipid-nucleic acid particles is effective (*see,* Declaration ¶13).

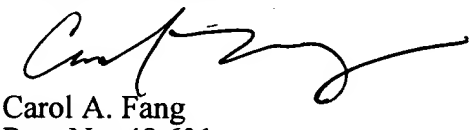
Therefore, a skilled artisan, using the teachings of the specification either alone or together with what is known to those of skill in the art, would be able to practice the invention as claimed, ***without*** undue experimentation.

In view of the foregoing remarks, Applicants assert that claims 1-28 are fully enabled by the specification as originally filed. Accordingly, Applicants respectfully request that the rejection under § 112, first paragraph, be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

35. (New) A method of treating a neoplasia in a mammal, in accordance with claim 5, wherein said gene encodes a suicide enzyme.

36. (New) A method of treating neoplasia in a mammal in accordance with claim 35, further comprising administering a prodrug.

37. (New) A method of treating a neoplasia in a mammal in accordance with claim 36, wherein said prodrug is administered after the serum stable nucleic acid-lipid particle.

38. (New) A method of treating a neoplasia in a mammal in accordance with claim 36, wherein said prodrug is administered before the serum stable nucleic acid-lipid particle.

39. (New) A method of treating a neoplasia in a mammal in accordance with claim 9, further comprising administering a chemotherapeutic agent.

40. (New) A method of treating a neoplasia in a mammal in accordance with claim 39, wherein the chemotherapeutic agent is administered after the serum stable nucleic acid-lipid particle.

41. (New) A method of treating a neoplasia in a mammal in accordance with claim 39, wherein the chemotherapeutic agent is administered before the serum stable nucleic acid-lipid particle.